ACTIVE AGENT DELIVERY SYSTEMS, MEDICAL DEVICES, AND METHODS

CROSS-REFERENCE TO RELATED APPLICATIONS

The present application claims priority to U.S. Provisional Patent Application Serial No. 60/403,352, filed on August 13, 2002, which is incorporated herein by reference in its entirety.

BACKGROUND OF THE INVENTION

A polymeric coating on a medical device may serve as a repository for delivery of an active agent (e.g., a therapeutic agent) to a subject. For many such applications, polymeric coatings must be as thin as possible. Polymeric materials for use in delivering an active agent may also be in various three-dimensional shapes.

Conventional active agent delivery systems suffer from limitations that include structural failure due to cracking and delamination from the device surface. Furthermore, they tend to be limited in terms of the range of active agents that can be used, the range of amounts of active agents that can be included within a delivery system, and the range of the rates at which the included active agents are delivered therefrom. This is frequently because many conventional systems include a single polymer.

Thus, there is a continuing need for active agent delivery systems with greater versatility and tunability.

SUMMARY OF THE INVENTION

The present invention provides active agent delivery systems that have generally good versatility and tunability in controlling the delivery of active agents. Typically, such advantages result from the use of a blend of two or more miscible polymers. These delivery systems can be

incorporated into medical devices, e.g., stents, stent grafts, anastomotic connectors, if desired.

The active agent delivery systems of the present invention typically include a blend of at least two miscible polymers, wherein at least one polymer (preferably one of the miscible polymers) is matched to the solubility of the active agent such that the delivery of the active agent preferably occurs predominantly under permeation control. In this context, "predominantly" with respect to permeation control means that at least 50%, preferably at least 75%, and more preferably at least 90%, of the total active agent load is delivered by permeation control.

Permeation control is typically important in delivering an active agent from systems in which the active agent passes through a miscible polymer blend having a "critical" dimension on a micron-scale level (i.e., the diffusion net path is no greater than about 1000 micrometers, although for shaped objects it can be up to about 10,000 microns). Furthermore, it is generally desirable to select polymers for a particular active agent that provide desirable mechanical properties without being detrimentally affected by nonuniform incorporation of the active agent.

In a first preferred embodiment, the present invention provides an active agent delivery system (having a target diffusivity) that includes an active agent and a miscible polymer blend, wherein: the active agent is hydrophobic and has a molecular weight of no greater than (i.e., less than or equal to) about 1200 g/mol; and the miscible polymer blend comprises at least two polymers, each with at least one solubility parameter, wherein: the difference between the solubility parameter of the active agent and at least one solubility parameter of at least one of the polymers is no greater than about 10 $J^{1/2}/cm^{3/2}$, and the difference between at least one solubility parameter of each of at least two polymers is no greater than about 5 $J^{1/2}/cm^{3/2}$; at least one polymer has an active agent diffusivity higher than the target diffusivity and at least one polymer has an active agent diffusivity lower than the target diffusivity; the molar average solubility parameter of the blend is no

greater than 28 $J^{1/2}/cm^{3/2}$ (preferably, no greater than 25 $J^{1/2}/cm^{3/2}$) and the swellability of the blend is no greater than 10% by volume.

In a second preferred embodiment, the present invention provides an active agent delivery system (having a target diffusivity) that includes an active agent and a miscible polymer blend, wherein: the active agent is hydrophilic and has a molecular weight of no greater than about 1200 g/mol; and the miscible polymer blend comprises at least two polymers, wherein: the difference between the solubility parameter of the active agent and at least one solubility parameter of at least one of the polymers is no greater than about 10 $J^{1/2}/cm^{3/2}$, and the difference between at least one solubility parameter of each of at least two polymers is no greater than about 5 $J^{1/2}/cm^{3/2}$; at least one polymer has an active agent diffusivity higher than the target diffusivity and at least one polymer has an active agent diffusivity lower than the target diffusivity; the molar average solubility parameter of the blend is greater than 21 $J^{1/2}/cm^{3/2}$ (preferably, greater than 25 $J^{1/2}/cm^{3/2}$); and the swellability of the blend is no greater than 10% by volume.

In a third preferred embodiment, the present invention provides an active agent delivery system (having a target diffusivity) that includes an active agent and a miscible polymer blend, wherein: the active agent is hydrophobic and has a molecular weight of greater than about 1200 g/mol; and the miscible polymer blend comprises at least two polymers, wherein: the difference between the solubility parameter of the active agent and at least one solubility parameter of at least one of the polymers is no greater than about 10 $J^{1/2}/cm^{3/2}$, and the difference between at least one solubility parameter of each of at least two polymers is no greater than about 5 $J^{1/2}/cm^{3/2}$; at least one polymer has an active agent diffusivity higher than the target diffusivity and at least one polymer has an active agent diffusivity lower than the target diffusivity; the molar average solubility parameter of the blend is no greater than 28 $J^{1/2}/cm^{3/2}$ (preferably, no greater than 25 $J^{1/2}/cm^{3/2}$); and the swellability of the blend is greater than 10% by volume.

In a fourth preferred embodiment, the present invention provides an active agent delivery system (having a target diffusivity) that includes an active agent and a miscible polymer blend, wherein: the active agent is hydrophilic and has a molecular weight of greater than about 1200 g/mol; and the miscible polymer blend comprises at least two polymers, wherein: the difference between the solubility parameter of the active agent and at least one solubility parameter of at least one of the polymers is no greater than about 10 $J^{1/2}/cm^{3/2}$, and the difference between at least one solubility parameter of each of at least two polymers is no greater than about 5 $J^{1/2}/cm^{3/2}$; at least one polymer has an active agent diffusivity higher than the target diffusivity and at least one polymer has an active agent diffusivity lower than the target diffusivity; the molar average solubility parameter of the blend is greater than 21 $J^{1/2}/cm^{3/2}$ (preferably, greater than 25 $J^{1/2}/cm^{3/2}$); and the swellability of the blend is greater than 10% by volume.

The present invention also provides medical devices that include such active agent delivery systems.

The present invention also provides methods for delivering an active agent to a subject. In one embodiment, a method of delivery includes: providing an active agent delivery system as described above and contacting the active agent delivery system with a bodily fluid, organ, or tissue of a subject.

The present invention also provides methods for designing (and making) an active agent delivery system for delivering an active agent over a preselected dissolution time (t) through a preselected critical dimension (x) of a miscible polymer blend.

In one embodiment, the method includes: providing an active agent having a molecular weight no greater than about 1200 g/mol; selecting at least two polymers, wherein: the difference between the solubility parameter of the active agent and at least one solubility parameter of each of the polymers is no greater than about 10 $J^{1/2}/cm^{3/2}$, and the difference between at least one solubility parameter of each of the at least two polymers is no greater than about 5 $J^{1/2}/cm^{3/2}$; and the

difference between at least one Tg of each of the at least two polymers is sufficient to include the target diffusivity; combining the at least two polymers to form a miscible polymer blend; and combining the miscible polymer blend with the active agent to form an active agent delivery system having the preselected dissolution time through a preselected critical dimension of the miscible polymer blend.

In another embodiment, the method includes: providing an active agent having a molecular weight greater than about 1200 g/mol; selecting at least two polymers, wherein: the difference between the solubility parameter of the active agent and at least one solubility parameter of each of the polymers is no greater than about 10 $J^{1/2}/cm^{3/2}$, and the difference between at least one solubility parameter of each of the at least two polymers is no greater than about 5 $J^{1/2}/cm^{3/2}$; and the difference between the swellabilities of the at least two polymers is sufficient to include the target diffusivity; combining the at least two polymers to form a miscible polymer blend; and combining the miscible polymer blend with the active agent to form an active agent delivery system having the preselected dissolution time through a preselected critical dimension of the miscible polymer blend.

The above summary of the present invention is not intended to describe each disclosed embodiment or every implementation of the present invention. The description that follows more particularly exemplifies illustrative embodiments. In several places throughout the application, guidance is provided through lists of examples, which examples can be used in various combinations. In each instance, the recited list serves only as a representative group and should not be interpreted as an exclusive list.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1. Chart of Tg versus solubility parameters of selected polymers. The box, centered at the solubility parameter of rosiglitazone maleate, encloses the candidates for rosiglitazone maleate.

Figure 2. Graph of the moduli of various poly(carbonate urethane) and poly(bis-phenol A carbonate) blends (PCU75D/PC blends) versus temperature. As the content of PC increased, the Tg of the individual polymers of the blends shifted closer together, indicating the PCU75D/PC blends were miscible.

Figure 3. Graph of the cumulative release of dexamethasone from various PCU75D/PC blends versus the square root of time. The release rates were tuned by changing the amount of PCU75D of the blends.

Figure 4. Graph of diffusion coefficient of dexamethasone in PCU75D/PC blends versus the composition of the blend. The diffusion coefficient increased as a function of the PCU75D content of the blends.

Figure 5. Graph of the cumulative release of dexamethasone from various PELLETHANE 75D/PX blends (PX = a linear poly(bis-phenol A epoxide resin, numbers after PL in the legend indicating the weight percent (wt-%) of PELLETHANE 75D in the blends) versus the square root of time. The release rates were tuned by changing the amount of PELLETHANE 75D of the blends.

Figure 6. DSC curves of PELLETHANE 75D/PHENOXY blends.

Figure 7. Graph of the cumulative release of dexamethasone from various PCU75D/PCU55D blends (blends of two different poly(carbonate urethane)s, numbers after PCU75D in the legend indicating the wt-% of PCU75D in the blends). The release rates were tuned by changing the amount of PCU55D of the blends.

Figure 8. Cumulative release of rosiglitasone maleate from various PELLETHANE 75D/PX blends (numbers after PL in the legend indicating the wt-% of PELLETHANE 75D in the blends). The release rates were tuned by changing the amount of PELLETHANE 75D of the blends.

Figure 9A-D. TSC scans of polyvinyl acetate and cellulose acetate butyrate blends (PVAC/CAB). The transition peaks shifted depending on the blend composition.

Figure 10. DSC scans of PVAC/CAB blends. The glass transitions of the blends changed as a function of the PVAC content of the blends.

Figure 11. Graph of cumulative release of dexamethasone from various PVAC/CAB blends versus the square root of time. The release rates were tuned by changing the amount of PVAC in the blends.

Figure 12. Graph of diffusion coefficient of dexamethasone in PVAC/CAB blends versus the composition of the blend. The diffusion coefficient increased as a function of the PVAC content of the blends.

Figure 13. Graph of the delivery of Resten NG from a blend of a hydrophilic polyurethane and a poly(vinyl acetate-co-vinyl pyrrolidone).

Figure 14. Graph of the DSC curves of TECOPHILIC HP-60D-60/PVP-VA blends.

Figure 15. Graph of the swelling percentage of TECOPHILIC HP-60D-60/PVP-VA blends as a function of PVP-VA content.

Figure 16. Graph showing the release profile of dexamethasone from a blend of 42 wt-% poly (ethylene-co-methyl acrylate) (PEcMA) and 58% poly (vinyl formal) (PVM). The release rate of dexamethasone from the polymer blend was between the rates of each of the unblended polymers, which demonstrates tunability of the blend system. The cumulative release was proportional to the square root of time, which demonstrates delivery by permeation control.

Figure 17. Graph showing the release profile of dexamethasone from a blend of 45 wt-% poly (ethylene-co-methyl acrylate) (PEcMA) and 55 wt-% polystyrene. The release rate of dexamethasone from the polymer blend was between the rates of each of the unblended polymers, which demonstrates tunability of the blend system. The cumulative release was proportional to square root of time, which demonstrates delivery by permeation control.

Figure 18. Graph showing the release profile of dexamethasone from a blend of 45 wt-% poly (ethylene-co-methyl acrylate) (PEcMA) and 55 wt-% poly(methyl methacrylate). The release rate of dexamethasone from the polymer blend was between the rates of each of the unblended

polymers, wihch demonstrates tunability of the blend system. The cumulative release was proportional to square root of time, which demonstrates delivery by permeation control.

Figure 19. Cumulative percentage release of coumarin from PL75D/TP blend cap-coated shims.

Figure 20. DSC curves of PL75D/TP blends that showed the miscibility between these two polymers.

DETAILED DESCRIPTION OF ILLUSTRATIVE EMBODIMENTS

The present invention provides active agent delivery systems that include an active agent for delivery to a subject and a miscible polymer blend. The delivery systems can include a variety of polymers as long as at least two are miscible as defined herein. The active agent may be incorporated within the miscible polymer blend such that it is dissoluted from the blend, or the blend can initially function as a barrier to the environment through which the active agent passes.

Miscible polymer blends are advantageous because they can provide greater versatility and tunability for a greater range of active agents than can conventional systems that include immiscible mixtures or only a single polymer, for example. That is, using two or more polymers, at least two of which are miscible, can generally provide a more versatile active agent delivery system than a delivery system with only one of the polymers. A greater range of types of active agents can typically be used. A greater range of amounts of an active agent can typically be incorporated into and delivered from (preferably, predominantly under permeation control) the delivery systems of the present invention. A greater range of delivery rates for an active agent can typically be provided by the delivery systems of the present invention. At least in part, this is because of the use of a miscible polymer blend that includes at least two miscible polymers. It should be understood that, although the description herein refers to two polymers, the invention encompasses systems that include more than two

polymers, as long as a miscible polymer blend is formed that includes at least two miscible polymers.

A miscible polymer blend of the present invention has a sufficient amount of at least two miscible polymers to form a continuous portion, which helps tune the rate of release of the active agent. Such a continuous portion (i.e., continuous phase) can be identified microscopically or by selective solvent etching. Preferably, the at least two miscible polymers form at least 50 percent by volume of a miscible polymer blend.

A miscible polymer blend can also optionally include a dispersed (i.e., discontinuous) immiscible portion. If both continuous and dispersed portions are present, the active agent can be incorporated within either portion. Preferably, the active agent is loaded into the continuous portion to provide delivery of the active agent predominantly under permeation control. To load the active agent, the solubility parameters of the active agent and the portion of the miscible polymer blend a majority of the active agent is loaded into are matched (typically to within no greater than about 10 $J^{1/2}/cm^{3/2}$, preferably, no greater than about 5 $J^{1/2}/cm^{3/2}$, and more preferably, no greater than about 3 $J^{1/2}/cm^{3/2}$). The continuous phase controls the release of the active agent regardless of where the active agent is loaded.

A miscible polymer blend, as used herein, encompasses a number of completely miscible blends of two or more polymers as well as partially miscible blends of two or more polymers. A completely miscible polymer blend will ideally have a single glass transition temperature (Tg), preferably one in each phase (typically a hard phase and a soft phase) for segmented polymers, due to mixing at the molecular level over the entire concentration range. Partially miscible polymer blends may have multiple Tg's, which can be in one or both of the hard phase and the soft phase for segmented polymers, because mixing at the molecular level is limited to only parts of the entire concentration range. These partially miscible blends are included within the scope of the term "miscible polymer blend" as long as the absolute

value of the difference in at least one Tg ($Tg_{polymer\ 1}$-$Tg_{polymer\ 2}$) for each of at least two polymers within the blend is reduced by the act of blending. Tg's can be determined by measuring the mechanical properties, thermal properties, electric properties, etc. as a function of temperature.

A miscible polymer blend can also be determined based on its optical properties. A completely miscible blend forms a stable and homogeneous domain that is transparent, whereas an immiscible blend forms a heterogeneous domain that scatters light and visually appears turbid unless the components have identical refractive indices. Additionally, a phase-separated structure of immiscible blends can be directly observed with microscopy. A simple method used in the present invention to check the miscibility involves mixing the polymers and forming a thin film of about 10 micrometers to about 50 micrometers thick. If such a film is generally as clear and transparent as the least clear and transparent film of the same thickness of the individual polymers prior to blending, then the polymers are completely miscible.

Miscibility between polymers depends on the interactions between them and their molecular structures and molecular weights. The interaction between polymers can be characterized by the so-called Flory-Huggins parameter (χ). When χ is close to zero (0) or even is negative, the polymers are very likely miscible. Theoretically, χ can be estimated from the solubility parameters of the polymers, i.e., χ is proportional to the squared difference between them. Therefore, the miscibility of polymers can be approximately predicted. For example, the closer the solubility parameters of the two polymers are the higher the possibility that the two polymers are miscible. Miscibility between polymers tends to decrease as their molecular weights increases.

Thus in addition to the experimental determinations, the miscibility between polymers can be predicted simply based on the Flory-Huggins interaction parameters, or even more simply, based the solubility parameters of the components. However, because of the molecular

weight effect, close solubility parameters do not necessarily guarantee miscibility.

It should be understood that a mixture of polymers needs only to meet one of the definitions provided herein to be miscible. Furthermore, a mixture of polymers may become a miscible blend upon incorporation of an active agent.Certain embodiments of the present invention includes segmented polymers. As used herein, a "segmented polymer" is composed of multiple blocks, each of which can separate into the phase that is primarily composed of itself. As used herein, a "hard" segment or "hard" phase of a polymer is one that is either crystalline at use temperature or amorphous with a glass transition temperature above use temperature (i.e., glassy), and a "soft" segment or "soft" phase of a polymer is one that is amorphous with a glass transition temperature below use temperature (i.e., rubbery). Herein, a "segment" refers to the chemical formulation and "phase" refers to the morphology, which primarily includes the corresponding segment (e.g., hard segments form a hard phase), but can include some of the other segment (e.g., soft segments in a hard phase).

As used herein, a "hard" phase of a blend includes primarily a segmented polymer's hard segment and optionally at least part of a second polymer blended therein. Similarly, a "soft" phase of a blend includes predominantly a segmented polymer's soft segment and optionally at least part of a second polymer blended therein. Preferably, miscible blends of polymers of the present invention include blends of segmented polymers' soft segments.

When referring to the solubility parameter of a segmented polymer, "segment" is used and when referring to Tg of a segmented polymer, "phase" is used. Thus, the solubility parameter, which is typically a calculated value for segmented polymers, refers to the hard and/or soft segment of an individual polymer molecule, whereas the Tg, which is typically a measured value, refers to the hard and/or soft phase of the bulk polymer.

The types and amounts of polymers and active agents are typically selected to form a system having a preselected dissolution time through a preselected critical dimension of the miscible polymer blend. Glass transition temperatures, swellabilities, and solubility parameters of the polymers can be used in guiding one of skill in the art to select an appropriate combination of components in an active agent delivery system, whether the active agent is incorporated into the miscible polymer blend or not. Solubility parameters are generally useful for determining miscibility of the polymers and matching the solubility of the active agent to that of the miscible polymer blend. Glass transition temperatures and/or swellabilities are generally useful for tuning the dissolution time (or rate) of the active agent. These concepts are discussed in greater detail below.

A miscible polymer blend can be used in combination with an active agent in the delivery systems of the present invention in a variety of formats as long as the miscible polymer blend controls the delivery of the active agent.

In one embodiment, a miscible polymer blend has an active agent incorporated therein. Preferably, such an active agent is dissoluted predominantly under permeation control, which requires at least some solubility of the active agent in the continuous portion (i.e., the miscible portion) of the polymer blend, whether the majority of the active agent is loaded in the continuous portion or not. Dispersions are acceptable as long as little or no porosity channeling occurs during dissolution of the active agent and the size of the dispersed domains is much smaller than the critical dimension of the blends, and the physical properties are generally uniform throughout the composition for desirable mechanical performance. This embodiment is often referred to as a "matrix" system.

In another embodiment, a miscible polymer blend initially provides a barrier to permeation of an active agent. This embodiment is often referred to as a "reservoir" system. A reservoir system can be in many formats with two or more layers. For example, a miscible polymer blend can form an outer layer over an inner layer of another material (referred

to herein as the inner matrix material). In another example, a reservoir system can be in the form of a core-shell, wherein the miscible polymer blend forms the shell around the core matrix (i.e., the inner matrix material). At least initially upon formation, the miscible polymer blend in the shell or outer layer could be substantially free of active agent. Subsequently, the active agent permeates from the inner matrix and through the miscible polymer blend for delivery to the subject. The inner matrix material can include a wide variety of conventional materials used in the delivery of active agents. These include, for example, an organic polymer such as those described herein for use in the miscible polymer blends, or a wax, or a different miscible polymer blend. Alternatively, the inner matrix material can be the active agent itself.

For a reservoir system, the release rate of the active agent can be tuned with selection of the material of the outer layer. The inner matrix can include an immiscible mixture of polymers or it can be a homopolymer if the outer layer is a miscible blend of polymers.

As with matrix systems, an active agent in a reservoir system is preferably dissoluted predominantly under permeation control through the miscible polymer blend of the barrier layer (i.e., the barrier polymer blend), which requires at least some solubility of the active agent in the barrier polymer blend. Again, dispersions are acceptable as long as little or no porosity channeling occurs in the barrier polymer blend during dissolution of the active agent and the size of the dispersed domains is much smaller than the critical dimension of the blends, and the physical properties are generally uniform throughout the barrier polymer blend for desirable mechanical performance. Although these considerations may also be desirable for the inner matrix, they are not necessary requirements.

Typically, the amount of active agent within an active agent delivery system of the present invention is determined by the amount to be delivered and the time period over which it is to be delivered. Other factors can also contribute to the level of active agent present, including,

for example, the ability of the composition to form a uniform film on a substrate.

Preferably, for a matrix system, an active agent is present within (i.e., incorporated within) a miscible polymer blend in an amount of at least about 0.1 weight percent (wt-%), more preferably, at least about 1 wt-%, and even more preferably, at least about 5 wt-%, based on the total weight of the miscible polymer blend and the active agent. Preferably, for a matrix system, an active agent is present within a miscible polymer blend in an amount of no greater than about 80 wt-%, more preferably, no greater than about 50 wt-%, and most preferably, no greater than about 30 wt-%, based on the total weight of the miscible polymer blend and the active agent. Typically and preferably, the amount of active agent will be at or below its solubility limit in the miscible polymer blend.

Preferably, for a reservoir system, an active agent is present within an inner matrix in an amount of at least about 0.1 wt-%, more preferably, at least about 10 wt-%, and even more preferably, at least about 25 wt-%, based on the total weight of the inner matrix (including the active agent). Preferably, for a reservoir system, an active agent is present within an inner matrix in an amount up to 100 wt-%, and more preferably, no greater than about 80 wt-%, based on the total weight of the inner matrix (including the active agent).

In the active agent delivery systems of the present invention, an active agent is dissolutable through a miscible polymer blend. Dissolution is preferably controlled predominantly by permeation of the active agent through the miscible polymer blend. That is, the active agent initially dissolves into the miscible polymer blend and then diffuses through the miscible polymer blend predominantly under permeation control. Thus, as stated above, for certain preferred embodiments, the active agent is at or below the solubility limit of the miscible polymer blend. Although not wishing to be bound by theory, it is believed that because of this mechanism the active agent delivery systems of the present invention have a significant level of tunability.

If the active agent exceeds the solubility of the miscible polymer blend and the amount of insoluble active agent exceeds the percolation limit, then the active agent could be dissoluted predominantly through a porosity mechanism. In addition, if the largest dimension of the active agent insoluble phase (e.g., particles or aggregates of particles) is on the same order as the critical dimension of the miscible polymer blend, then the active agent could be dissoluted predominantly through a porosity mechanism. Dissolution by porosity control is typically undesirable because it does not provide effective predictability and controllability.

Because the active agent delivery systems of the present invention preferably have a critical dimension on the micron-scale level, it can be difficult to include a sufficient amount of active agent and avoid delivery by a porosity mechanism. Thus, the solubility parameters of the active agent and at least one polymer of the miscible polymer blend are matched to maximize the level of loading while decreasing the tendency for delivery by a porosity mechanism.

One can determine if there is a permeation-controlled release mechanism by examining a dissolution profile of the amount of active agent released versus time (t). For permeation-controlled release from a matrix system, the profile is directly proportional to $t^{1/2}$. For permeation-controlled release from a reservoir system, the profile is directly proportional to t. Alternatively, under sink conditions (i.e., conditions under which there are no rate-limiting barriers between the polymer blend and the media into which the active agent is dissoluted), porosity-controlled dissolution could result in a burst effect (i.e., an initial very rapid release of active agent).

The active agent delivery systems of the present invention, whether in the form of a matrix system or a reservoir system, for example, without limitation, can be in the form of coatings on substrates (e.g., open or closed cell foams, woven or nonwoven materials), films (which can be free-standing as in a patch, for example), shaped objects

(e.g., microspheres, beads, rods, fibers, or other shaped objects), wound packing materials, etc.

As used herein, an "active agent" is one that produces a local or systemic effect in a subject (e.g., an animal). Typically, it is a pharmacologically active substance. The term is used to encompass any substance intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease or in the enhancement of desirable physical or mental development and conditions in a subject. The term "subject" used herein is taken to include humans, sheep, horses, cattle, pigs, dogs, cats, rats, mice, birds, reptiles, fish, insects, arachnids, protists (e.g., protozoa), and prokaryotic bacteria. Preferably, the subject is a human or other mammal.

Active agents can be synthetic or naturally occurring and include, without limitation, organic and inorganic chemical agents, polypeptides (which is used herein to encompass a polymer of L- or D- amino acids of any length including peptides, oligopeptides, proteins, enzymes, hormones, etc.), polynucleotides (which is used herein to encompass a polymer of nucleic acids of any length including oligonucleotides, single- and double-stranded DNA, single- and double-stranded RNA, DNA/RNA chimeras, etc.), saccharides (e.g., mono-, di-, poly-saccharides, and mucopolysaccharides), vitamins, viral agents, and other living material, radionuclides, and the like. Examples include antithrombogenic and anticoagulant agents such as heparin, coumadin, coumarin, protamine, and hirudin; antimicrobial agents such as antibiotics; antineoplastic agents and anti-proliferative agents such as etoposide, podophylotoxin; antiplatelet agents including aspirin and dipyridamole; antimitotics (cytotoxic agents) and antimetabolites such as methotrexate, colchicine, azathioprine, vincristine, vinblastine, fluorouracil, adriamycin, and mutamycinnucleic acids; antidiabetic such as rosiglitazone maleate; and anti-inflammatory agents. Anti-inflammatory agents for use in the present invention include glucocorticoids, their salts, and derivatives thereof, such as cortisol, cortisone, fludrocortisone, Prednisone, Prednisolone, 6α-methylprednisolone, triamcinolone, betamethasone,

dexamethasone, beclomethasone, aclomethasone, amcinonide, clebethasol and clocortolone. Preferably, the active agent is not heparin.

For preferred active agent delivery systems of the present invention, the active agent is typically matched to the solubility of the miscible portion of the polymer blend. Thus, for embodiments of the invention in which the active agents are hydrophilic, preferably at least one miscible polymer of the miscible polymer blend is hydrophilic. For embodiments of the invention in which the active agents are hydrophobic, preferably at least one miscible polymer of the miscible polymer blend is hydrophobic. However, this is not necessarily required, and it may be undesirable to have a hydrophilic polymer in a delivery system for a low molecular weight hydrophilic active agent because of the potential for swelling of the polymers by water and the loss of controlled delivery of the active agent.As used herein, in this context (in the context of the polymer of the blend), the term "hydrophilic" refers to a material that will increase in volume by more than 10% or in weight by at least 10%, whichever comes first, when swollen by water at body temperature (i.e., about 37°C). As used herein, in this context (in the context of the polymer of the blend), the term "hydrophobic" refers to a material that will not increase in volume by more than 10% or in weight by more than 10%, whichever comes first, when swollen by water at body temperature (i.e., about 37°C).

As used herein, in this context (in the context of the active agent), the term “hydrophilic” refers to an active agent that has a solubility in water of more than 200 micrograms per milliliter. As used herein, in this context (in the context of the active agent), the term “hydrophobic” refers to an active agent that has a solubility in water of no more than 200 micrograms per milliliter.

As the size of the active agent gets sufficiently large, diffusion through the polymer is affected. Thus, active agents can be categorized based on molecular weights and polymers can be selected depending on the range of molecular weights of the active agents.

For certain preferred active agent delivery systems of the present invention, the active agent has a molecular weight of greater than about 1200 g/mol. For certain other preferred active agent delivery systems of the present invention, the active agent has a molecular weight of no greater than (i.e., less than or equal to) about 1200 g/mol. For even more preferred embodiments, active agents of a molecular weight no greater than about 800 g/mol are desired.

Once the active agent and the format for delivery (e.g., time/rate and critical dimension) are selected, one of skill in the art can utilize the teachings of the present invention to select the appropriate combination of at least two polymers to provide an active agent delivery system.

As stated above, the types and amounts of polymers and active agents are typically selected to form a system having a preselected dissolution time (t) through a preselected critical dimension (x) of the miscible polymer blend. This involves selecting at least two polymers to provide a target diffusivity, which is directly proportional to the critical dimension squared divided by the time (x^2/t), for a given active agent.

In refining the selection of the polymers for the desired active agent, the desired dissolution time (or rate), and the desired critical dimension, the parameters that can be considered when selecting the polymers for the desired active agent include glass transition temperatures of the polymers, swellabilities of the polymers, solubility parameters of the polymers, and solubility parameters of the active agents. These can be used in guiding one of skill in the art to select an appropriate combination of components in an active agent delivery system, whether the active agent is incorporated into the miscible polymer blend or not.

For enhancing the versatility of a permeation-controlled delivery system, for example, preferably the polymers are selected such that at least one of the following relationships is true: (1) the difference between the solubility parameter of the active agent and at least one solubility parameter of at least one polymer is no greater than about 10 $J^{1/2}/cm^{3/2}$ (preferably, no greater than about 5 $J^{1/2}/cm^{3/2}$, and more

preferably, no greater than about 3 $J^{1/2}/cm^{3/2}$); and (2) the difference between at least one solubility parameter of each of at least two polymers is no greater than about 5 $J^{1/2}/cm^{3/2}$ (preferably, no greater than about 3 $J^{1/2}/cm^{3/2}$). More preferably, both relationships are true. Most preferably, both relationships are true for all polymers of the blend.

Typically, a compound has only one solubility parameter, although certain polymers, such as segmented copolymers and block copolymers, for example, can have more than one solubility parameter. Solubility parameters can be measured or they are calculated using an average of the values calculated using the Hoy Method and the Hoftyzer-van Krevelen Method (chemical group contribution methods), as disclosed in D.W. van Krevelen, Properties of Polymers, 3rd Edition, Elsevier, Amsterdam. To calculate these values, the volume of each chemical is needed, which can be calculated using the Fedors Method, disclosed in the same reference.

Solubility parameters can also be calculated with computer simulations, for example, molecular dynamics simulation and Monte Carlo simulation. Specifically, the molecular dynamics simulation can be conducted with Accelrys Materials Studio, Accelrys Inc., San Diego, CA. The computer simulations can be used to directly calculate the Flory-Huggins parameter.

Examples of solubility parameters for various polymers and active agents is shown in Table 1.

Table 1

Polymers	Solubility parameter ($J^{1/2}/cm^{3/2}$)	Source	Notes	Tg (°C)	Notes	Source
polyethylene	16.45	1		-94		1
polypropylene	17.8	1		-10	Isotactic	1
polyisobutylene	16.3	1		-71.5		1
polystyrene	18.2	1		102.5	Atactic	1
poly(vinyl chloride)	20.65	1		84		1
poly(vinyl bromide)	19.4	1				
poly(vinylidene chloride)	22.65	1		-1.5		2
poly(tetrafluoroethylene)	12.7	1		27.5		1
poly(chloro trifluoroethylene)	15.45	1		45		1
poly(vinyl alcohol)	27.45	1		85		1
poly(vinyl acetate)	20.85	1		28		1
poly(vinyl propionate)	18	1				
poly(methyl acylate)	20.6	1		4.5		1
poly(ethyl acrylate)	19	1		-24		1

poly(propyl acrylate)	18.5	1				
poly(butyl acrylate)	18.3	1		-56		1
poly(isobutyl acrylate)	20.15	1				
poly(2,2,3,3,4,4,4-heptafluorobutyl acrylate)	13.7	1				
poly(methyl methacrylate)	22.4	1		105	Atactic	1
poly(ethyl methacrylate)	18.45	1		65		1
poly(butyl methacrylate)	18.1	1		21		1
poly(isobutyl methacrylate)	19.15	1				
poly(tert-butyl methacrylate)	17	1				
poly(benzyl methacrylate)	20.3	1				
poly(ethoxyethyl methacrylate)	19.35	1				
polyacrylonitrile	28.55	1		117	Syndiotactic,	1
polymethacrylonitrile	21.9	1		120		1
poly(alpha-cyanomethyl acrylate)	29.2	1				

polybutadiene	17.1	1		-50.5	Trans 1,4-butadiene	1
polyisoprene	18.35	1		-59	Trans	1
polychloroprene	17.85	1				
polyformaldehyde	21.7	1		-66.5		1
poly(tetramethylene oxide)	17.25	1		-83.5		2
poly(propylene oxide)	17.85	1				
polyepichlorohydrin	19.2	1				
poly(ethylene sulphide)	18.8	1				
poly(styrene sulphide)	19	1				
poly(ethylene terephthalate)	20.9	1		69		1
poly(8-aminocaprylic acid)	26	1				
poly(hexamethylene adipamide)	27.8	1				
polyurethane hard segment (MDI + BDO)	23.35	2	H-vK, urethane NHCOO = NH + COO. Fedors volume 230 cm^3/mol	10		RSA
poly(bisphenyl A carbonate)	22.9	2	H-vK, carbonate OCOO =	140		1

			COO + O; Hoy OCOO=O + COO. Fedors volume 174 cm^3/mol			
cellulose acetate butyrate (acetyl 29.5 wt-%, butyryl 17 wt-%)	21.8	2	The total numbers of acetyl, butyryl, and OH has to be 3 per repeat unit. It was estimated the wt-% of OH was 1.1 and the molecular weight of the repeat unit was 303 g/mol. Fedors volume 188 cm^3/mol	110		TSC
phenoxy	23.2	2	Fedors volume 201 cm^3/mol	95		Vendor
poly(vinyl pyrrolidone)	25.1	2	CON = CO + tertiary N. Fedors volume 65 cm^3/mol	175		1
poly(vinyl pyrrolidone) co poly (vinyl acetate) (1.3/1 wt)	21.7	2	CON = CO + tertiary N. Fedors volume 132 cm^3/mol			
poly(ethylene oxide)	22.15	2	Fedors volume 36 cm^3/mol	-47		2
dexamethasone	27.25	2	All rings were treated as			

			aliphatic. Hydroxyl groups were not involved in hydrogen bonding. Fedors volume 205 cm^3/mol			
rosiglitazone maleate	23.45	2	H-vK, C5NH5 as C6H5*5/6 + tertiary N, CONHCO as 2CO + NH; Hoy, aromatic tertiary N treated as aliphatic tertiary N, CONHCO as CONH + CO. Fedors volume 306 cm^3/mol			

Source for Solubility Parameters:

1. D.W.van Krevelen, Properties of Polymers, 3rd ed., Elsevier, 1990. Table 7.5. Data were the average if there were two values listed in the sources.
2. Average of the calculated values based on Hoftyzer and van Kevelen's (H-vK) method (where the volumes of the chemicals were calculated based on Fedors' method) and Hoy's method. See Chapter 7, D.W.van Krevelen, Properties of Polymers, 3rd ed., Elsevier,1990, for details of all the calculations, where Table 7.8 was for Hoftyzer and van Kevelen's method, Table 7.3 for Fedors' method, and Table 7.9 and 7.10 for Hoy's method.

Source of Tg's (the reported value is the average if there are two values listed in the sources):

1. Table 6.6, J. M. He, W. X. Chen, and X. X. Dong, Polymer Physics, revised version, FuDan University Press, ShangHai, China, 2000. Data were the average if there were two values listed in the sources.
2. Table 6.4, D.W.van Krevelen, Properties of Polymers, 3rd ed., Elsevier,1990. Data were the average if there were two values listed in the sources.

For delivery systems in which the active agent is hydrophobic, regardless of the molecular weight, polymers are typically selected such that the molar average solubility parameter of the miscible polymer blend is no greater than 28 $J^{1/2}/cm^{3/2}$ (preferably, no greater than 25 $J^{1/2}/cm^{3/2}$). Herein "molar average solubility parameter" means the average of the solubility parameters of the blend components that are miscible with each other and that form the continuous portion of the miscible polymer blend. These are weighted by their molar percentage in the blend, without the active agent incorporated into the polymer blend.

For example, for a hydrophobic active agent of no greater than about 1200 g/mol, such as dexamethasone, which has a solubility parameter of 27 $J^{1/2}/cm^{3/2}$, based on Group Contribution Methods or 21 $J^{1/2}/cm^{3/2}$ based on Molecular Dynamics Simulations, an exemplary polymer blend includes cellulose acetate butyrate (CAB) and polyvinyl acetate (PVAC). These have solubility parameters of 22 $J^{1/2}/cm^{3/2}$ and 21 $J^{1/2}/cm^{3/2}$, respectively. A suitable blend of these polymers (1:1 molar ratio is CAB to PVAC) has a molar average solubility parameter of 21.5 $J^{1/2}/cm^{3/2}$. This value was calculated as described herein as 22 *0.5 +21*0.5 = 21.5 ($J^{1/2}/cm^{3/2}$). The molecular weight of the repeat unit of CAB is estimated to be 303 g/mol based on the fact that the total number of the acetyl, butyryl, and OH groups has to be 3 per repeat unit. The molecular weight of the repeat unit of PVAC is 86 g/mol. Then the weight ratio of the CAB to PVAC = 0.78/0.22 for this 1:1 molar ratio blend.

For delivery systems in which the active agent is hydrophilic, regardless of the molecular weight, polymers are typically selected such that the molar average solubility parameter of the miscible polymer blend is greater than 21 $J^{1/2}/cm^{3/2}$ (preferably, greater than 25 $J^{1/2}/cm^{3/2}$).

For enhancing the tunability of permeation-controlled dissolution times (rates) for low molecular weight active agents, preferably the polymers can be selected such that the difference between at least one Tg of at least two of the polymers corresponds to a range of diffusivities that includes the target diffusivity.

Alternatively, for enhancing the tunability of permeation-controlled dissolution times (rates) for high molecular weight active agents, preferably the polymers can be selected such that the difference between the swellabilities of at least two of the polymers of the blend corresponds to a range of diffusivities that includes the target diffusivity. The target diffusivity is determined by the preselected time (t) for delivery and the preselected critical dimension (x) of the polymer composition and is directly proportional to x^2/t.

The target diffusivity can be easily measured by dissolution analysis using the following equation (see, for example, Kinam Park edited, Controlled Drug Delivery: Challenges and Strategies, American Chemical Society, Washington, DC, 1997):

$$D = \left(\frac{M_t}{4M_\infty}\right)^2 \cdot \frac{\pi x^2}{t}$$

wherein D = diffusion coefficient; M_t = cumulative release; M_∞ = total loading of active agent; x = the critical dimension (e.g., thickness of the film); and t = the dissolution time. This equation is valid during dissolution of up to 60 percent by weight of the initial load of the active agent. Also, blend samples should be in the form of a film.

Generally, at least one polymer has an active agent diffusivity higher than the target diffusivity and at least one polymer has an active agent diffusivity lower than the target diffusivity. The diffusivity of a polymer system can be easily measured by dissolution analysis, which is described in greater detail in the Examples Section. The diffusivity of an active agent from each of the individual polymers can be determined by dissolution analysis, but can be estimated by relative Tg's or swellabilities of the major phase of each polymer.

The diffusivity can be correlated to glass transition temperatures of hydrophobic or hydrophilic polymers, which can be used to design a delivery system for low molecular weight active agents (e.g., those

having a molecular weight of no greater than about 1200 g/mol). Alternatively, the diffusivity can be correlated to swellabilities of hydrophobic or hydrophilic polymers, which can be used to design a delivery system for high molecular weight polymers (e.g., those having a molecular weight of greater than about 1200 g/mol). This is advantageous because the range of miscible blends can be used to encompass very different dissolution rates for active agents of similar solubility.

The glass transition temperature of a polymer is a well-known parameter, which is typically a measured value. Exemplary values are listed in Table 1. For segmented polymers (e.g., a segmented polyurethane) the Tg refers to the particular phase of the bulk polymer. Typically, for low molecular weight active agents, by selecting relatively low and high Tg polymers that are miscible, the dissolution kinetics of the system can be tuned. This is because a small molecular weight agent (e.g., no greater than about 1200 g/mol) diffuses through a path that is directly correlated with the Tg's, i.e., the free volume of the polymer blend is a linear function of the temperature with slope being greater when the temperature is above Tg.

Preferably, a polymer having at least one relatively high Tg is combined with a polymer having at least one relatively low Tg.

For example, a miscible polymer blend for an active agent having a molecular weight of no greater than 1200 g/mol includes cellulose acetate butyrate, which has a Tg of 100-120°C, and polyvinyl acetate, which has a Tg of 20-30°C. Another example of a miscible polymer blend for an active agent having a molecular weight of no greater than 1200 g/mol includes a polyurethane with a hard phase Tg of about 10-80°C and a polycarbonate with a Tg of about 140°C. By combining such high and low Tg polymers, the active agent delivery system can be tuned for the desired dissolution time of the active agent.

Figure 1 shows suitable polymer candidates for a miscible polymer blend for delivering a low molecular weight hydrophobic active agent, rosiglitazone maleate. This is a chart of Tg versus solubility

parameters of selected polymers. The box, centered at the solubility parameter of rosiglitazone maleate, encloses the candidates for this active agent.

Swellabilities of polymers in water can be easily determined. It should be understood, however, that the swellability results from incorporation of water and not from an elevation in temperature. Typically, for high molecular weight active agents, by selecting relatively low and high swell polymers that are miscible, the dissolution kinetics of the system can be tuned. Swellabilities of polymers are used to design these systems because water needs to diffuse into the polymer blend to increase the free volume for active agents of relatively high molecular weight (e.g., greater than about 1200 g/mol) to diffuse out of the polymeric blend.

Preferably, a polymer having a relatively high swellability is combined with a polymer having a relatively low swellability. For example, a miscible polymer blend for an active agent having a molecular weight of greater than 1200 g/mol includes polyvinyl pyrollidone-vinyl acetate copolymer, which has a swellability of greater than 100% (i.e., it is water soluble), and poly(ether urethane), which has a swellability of 60%. By combining such high and low swell polymers, the active agent delivery system can be tuned for the desired dissolution time of the active agent.

Swellabilities of the miscible polymer blends are also used as a factor in determining the combinations of polymers for a particular active agent. For delivery systems in which the active agent has a molecular weight of greater than 1200 g/mol, whether it is hydrophilic or hydrophobic, polymers are selected such that the swellability of the blend is greater than 10% by volume. The swellability of the blend is evaluated without the active agent incorporated therein.

For a first group of active agents that are hydrophobic and have a molecular weight of no greater than about 1200 g/mol, the polymers for the miscible polymer blend are selected such that: the average molar solubility parameter of the miscible polymers of the blend is no greater

than 28 $J^{1/2}/cm^{3/2}$ (preferably, no greater than 25 $J^{1/2}/cm^{3/2}$); and the swellability of the blend is no greater than 10% by volume.

Examples of suitable combinations of polymer blends for the first group of active agents are described in greater detail in Applicants' Assignee's copending applications entitled: ACTIVE AGENT DELIVERY SYSTEM INCLUDING A HYDROPHOBIC CELLULOSE DERIVATIVE, MEDICAL DEVICE, AND METHOD, having U.S. Provisional Patent Application Serial No. 60/403,477, filed on August 13, 2002, and U.S. Patent Application Serial No. _____, filed on even date herewith; ACTIVE AGENT DELIVERY SYSTEM INCLUDING A POLYURETHANE, MEDICAL DEVICE, AND METHOD, having U.S. Provisional Patent Application Serial No. 60/403,478, filed on August 13, 2002, and U.S. Patent Application Serial No. _____, filed on even date herewith; and ACTIVE AGENT DELIVERY SYSTEM INCLUDING A POLY(ETHYLENE-CO-(METH)ACRYLATE), MEDICAL DEVICE, AND METHOD, having U.S. Provisional Patent Application Serial No. 60/403,413, filed on August 13, 2002, and U.S. Patent Application Serial No. _____, filed on even date herewith. Specific examples of such blends are illustrated in the Examples Section. Preferably, the miscible polymer blend suitable for use with the first group of active agents does not include the following: a blend of a hydrophobic cellulose derivative and a polyurethane or polyvinyl pyrrolidone; and/or a blend of a polyalkyl methacrylate and a polyethylene-co-vinyl acetate.

For a second group of active agents that are hydrophilic and have a molecular weight of no greater than about 1200 g/mol, the polymers for the miscible polymer blend are selected such that: the molar average solubility parameter of the blend is greater than 21 $J^{1/2}/cm^{3/2}$ (preferably, greater than 25 $J^{1/2}/cm^{3/2}$); and the swellability of the blend is no greater than 10% by volume.

Examples of suitable polymers for systems that deliver an active agent from this second group include polyacrylonitriles, cyanoacrylates, methacrylonitriles, hydrophilic cellulosics, and the like, and combinations

thereof. In this context, "combination" means mixtures and copolymers thereof. The mixtures and copolymers can include one or more members of the group and/or other monomers/polymers. Preferably, the miscible polymer blend suitable for use with the second group of active agents does not include both a hydrophobic cellulose derivative and a polyvinyl pyrrolidone.

Examples of suitable combinations of polymer blends for the first group of active agents are described in greater detail in Applicants' Assignee's copending application entitled ACTIVE AGENT DELIVERY SYSTEM INCLUDING A POLYURETHANE, MEDICAL DEVICE, AND METHOD, having U.S. Patent Application Serial No. _____, filed on even date herewith.

For a third group of active agents that are hydrophobic and have a molecular weight of greater than about 1200 g/mol, the polymers for the miscible polymer blend are selected such that: the molar average solubility parameter of the blend is no greater than 28 $J^{1/2}/cm^{3/2}$ (preferably, no greater than 25 $J^{1/2}/cm^{3/2}$); and the swellability of the blend is greater than 10% by volume.

Examples of suitable polymers for systems that deliver an active agent from this third group include at least one hydrophobic polymer including hydrophobic cellulose derivatives such as methyl cellulose, ethyl cellulose, hydroxy propyl cellulose, cellulose acetate, cellulose propionate, cellulose butyrate, cellulose nitrate, hydroxypropyl methyl cellulose, hydroxypropyl ethyl cellulose, methyl ethyl cellulose, cellulose acetate propionate, cellulose acetate butyrate, cellulose propionate butyrate, cellulose acetate propionate butyrate, and combinations thereof. The polymer blends for these systems can include a second polymer that is either hydrophobic or hydrophilic. For example, the hydrophilic polymer can be a hydrophilic polyurethane. A preferred hydrophilic polyurethane includes soft segments having therein polyethylene oxide units. Examples of suitable hydrophilic polyurethanes are poly(ether urethanes) available from Thermedics, Inc. (Woburn, MA), under the tradename TECOPHILIC. Preferably, the

miscible polymer blend suitable for use with the third group of active agents does not include the following: a blend of a hydrophobic cellulose derivative and a polyurethane or polyvinyl pyrrolidone; and/or a blend of a polyalkyl methacrylate and a polyethylene-co-vinyl acetate.

For a fourth group of active agents that are hydrophilic and have a molecular weight of greater than about 1200 g/mol, the polymers for the miscible polymer blend are selected such that: the molar average solubility parameter of the blend is greater than 21 $J^{1/2}/cm^{3/2}$ (preferably, greater than 25 $J^{1/2}/cm^{3/2}$); and the swellability of the blend is greater than 10% by volume.

Examples of suitable combinations of polymer blends for the fourth group of active agents are described in greater detail in Applicants' Assignee's copending applications entitled ACTIVE AGENT DELIVERY SYSTEM INCLUDING A HYDROPHILIC POLYMER, MEDICAL DEVICE, AND METHOD (Attorney Docket No. P-10858.00), having U.S. Provisional Patent Application Serial No. 60/403,392, filed on August 13, 2002, and U.S. Patent Application Serial No. _____, filed on even date herewith. Specific examples of such blends are illustrated in the Examples Section. Preferably, the miscible polymer blend suitable for use with the fourth group of active agents does not include both a hydrophobic cellulose derivative and a polyvinyl pyrrolidone.

The polymers in the miscible polymer blends can be crosslinked or not. Similarly, the blended polymers can be crosslinked or not. Such crosslinking can be carried out by one of skill in the art after blending using standard techniques.

In the active agent systems of the present invention, the active agent passes through a miscible polymer blend having a "critical" dimension. This critical dimension is along the net diffusion path of the active agent and is preferably no greater than about 1000 micrometers (i.e., microns), although for shaped objects it can be up to about 10,000 microns.

For embodiments in which the miscible polymer blends form coatings or free-standing films (both generically referred to herein as "films"), the critical dimension is the thickness of the film and is preferably no greater than about 1000 microns, more preferably no greater than about 500 microns, and most preferably no greater than about 100 microns. A film can be as thin as desired (e.g., 1 nanometer), but are preferably no thinner than about 10 nanometers, more preferably no thinner than about 100 nanometers. Generally, the minimum film thickness is determined by the volume that is needed to hold the required dose of active agent and is typically only limited by the process used to form the materials. For all embodiments herein, the thickness of the film does not have to be constant or uniform. Furthermore, the thickness of the film can be used to tune the duration of time over which the active agent is released.

For embodiments in which the miscible polymer blends form shaped objects (e.g., microspheres, beads, rods, fibers, or other shaped objects), the critical dimension of the object (e.g., the diameter of a microsphere or rod) is preferably no greater than about 10,000 microns, more preferably no greater than about 1000 microns, even more preferably no greater than about 500 microns, and most preferably no greater than about 100 microns. The objects can be as small as desired (e.g., 10 nanometers for the critical dimension). Preferably, the critical dimension is no less than about 100 microns, and more preferably no less than about 500 nanometers.

In one embodiment, the present invention provides a medical device characterized by a substrate surface overlayed with a polymeric top coat layer that includes a miscible polymer blend, preferably with a polymeric undercoat (primer) layer. When the device is in use, the miscible polymer blend is in contact with a bodily fluid, organ, or tissue of a subject.

The invention is not limited by the nature of the medical device; rather, any medical device can include the polymeric coating layer that includes the miscible polymer blend. Thus, as used herein, the term

"medical device" refers generally to any device that has surfaces that can, in the ordinary course of their use and operation, contact bodily tissue, organs or fluids such as blood. Examples of medical devices include, without limitation, stents, stent grafts, anastomotic connectors, leads, needles, guide wires, catheters, sensors, surgical instruments, angioplasty balloons, wound drains, shunts, tubing, urethral inserts, pellets, implants, pumps, vascular grafts, valves, pacemakers, and the like. A medical device can be an extracorporeal device, such as a device used during surgery, which includes, for example, a blood oxygenator, blood pump, blood sensor, or tubing used to carry blood, and the like, which contact blood which is then returned to the subject. A medical device can likewise be an implantable device such as a vascular graft, stent, stent graft, anastomotic connector, electrical stimulation lead, heart valve, orthopedic device, catheter, shunt, sensor, replacement device for nucleus pulposus, cochlear or middle ear implant, intraocular lens, and the like. Implantable devices include transcutaneous devices such as drug injection ports and the like.

In general, preferred materials used to fabricate the medical device of the invention are biomaterials. A "biomaterial" is a material that is intended for implantation in the human body and/or contact with bodily fluids, tissues, organs and the like, and that has the physical properties such as strength, elasticity, permeability and flexibility required to function for the intended purpose. For implantable devices in particular, the materials used are preferably biocompatible materials, i.e., materials that are not overly toxic to cells or tissue and do not cause undue harm to the body.

The invention is not limited by the nature of the substrate surface for embodiments in which the miscible polymer blends form polymeric coatings. For example, the substrate surface can be composed of ceramic, glass, metal, polymer, or any combination thereof. In embodiments having a metal substrate surface, the metal is typically iron, nickel, gold, cobalt, copper, chrome, molybdenum, titanium, tantalum, aluminum, silver, platinum, carbon, and alloys thereof. A

preferred metal is stainless steel, a nickel titanium alloy, such as NITINOL, or a cobalt chrome alloy, such as NP35N.

A polymeric coating that includes a miscible polymer blend can adhere to a substrate surface by either covalent or non-covalent interactions. Non-covalent interactions include ionic interactions, hydrogen bonding, dipole interactions, hydrophobic interactions and van der Waals interactions, for example.

Preferably, the substrate surface is not activated or functionalized prior to application of the miscible polymer blend coating, although in some embodiments pretreatment of the substrate surface may be desirable to promote adhesion. For example, a polymeric undercoat layer (i.e., primer) can be used to enhance adhesion of the polymeric coating to the substrate surface. Suitable polymeric undercoat layers are disclosed in Applicants' Assignee's copending U.S. Provisional Application Serial No. 60/403,479, filed on August 13, 2002, and U.S. Patent Application Serial No. _____, filed on even date herewith, both entitled MEDICAL DEVICE EXHIBITING IMPROVED ADHESION BETWEEN POLYMERIC COATING AND SUBSTRATE. A particularly preferred undercoat layer disclosed therein consists essentially of a polyurethane. Such a preferred undercoat layer includes a polymer blend that contains polymers other than polyurethane but only in amounts so small that they do not appreciably affect the durometer, durability, adhesive properties, structural integrity and elasticity of the undercoat layer compared to an undercoat layer that is exclusively polyurethane.

When a stent or other vascular prosthesis is implanted into a subject, restenosis is often observed during the period beginning shortly after injury to about four to six months later. Thus, for embodiments of the invention that include stents, the generalized dissolution rates contemplated are such that the active agent should ideally start to be released immediately after the prosthesis is secured to the lumen wall to lessen cell proliferation. The active agent should then continue to dissolute for up to about four to six months in total.

The invention is not limited by the process used to apply the polymer blends to a substrate surface to form a coating. Examples of suitable coating processes include solution processes, powder coating, melt extrusion, or vapor deposition.

A preferred method is solution coating. For solution coating processes, examples of solution processes include spray coating, dip coating, and spin coating. Typical solvents for use in a solution process include tetrahydrofuran (THF), methanol, ethanol, ethylacetate, dimethylformamide (DMF), dimethyacetamide (DMA), dimethylsulfoxide (DMSO), dioxane, N-methyl pyrollidone, chloroform, hexane, heptane, cyclohexane, toluene, formic acid, acetic acid, and/or dichloromethane. Single coats or multiple thin coats can be applied.

Similarly, the invention is not limited by the process used to form the miscible polymer blends into shaped objects. Such methods would depend on the type of shaped object. Examples of suitable processes include extrusion, molding, micromachining, emulsion polymerization methods, electrospray methods, etc.

For preferred embodiments in which the active agent delivery system includes one or more coating layers applied to a substrate surface, a preferred embodiment includes the use of a primer, which is preferably applied using a "reflow method," which is described in Applicants' Assignee's copending U.S. Provisional Application Serial No. 60/403,479, filed on August 13, 2002, and U.S. Patent Application Serial No. _____, filed on even date herewith, both entitled MEDICAL DEVICE EXHIBITING IMPROVED ADHESION BETWEEN POLYMERIC COATING AND SUBSTRATE.

Preferably, in this "reflow method," the device fabrication process involves first applying an undercoat polymer to a substrate surface to form the polymeric undercoat layer, followed by treating the polymeric undercoat layer to reflow the undercoat polymer, followed by applying a miscible polymer blend, preferably with an active agent incorporated therein, to the reformed undercoat layer to form a polymeric top coat layer. Reflow of the undercoat polymer can be accomplished in any

convenient manner, e.g., thermal treatment, infrared treatment, ultraviolet treatment, microwave treatment, RF treatment, mechanical compression, or solvent treatment. To reflow the undercoat polymer, the undercoat layer is heated to a temperature that is at least as high as the "melt flow temperature" of the undercoat polymer, and for a time sufficient to reflow the polymer. The temperature at which the polymer enters the liquid flow state (i.e., the "melt flow temperature") is the preferred minimum temperature that is used to reflow the polymer according to the invention. Typically 1 to 10 minutes is the time period used to reflow the polymer using a thermal treatment in accordance with the invention. The melt flow temperature for a polymer is typically above the Tg (the melt temperature for a glass) and the Tm (the melt temperature of a crystal) of the polymer.

EXAMPLES

The present invention is illustrated by the following examples. It is to be understood that the particular examples, materials, amounts, and procedures are to be interpreted broadly in accordance with the scope and spirit of the invention as set forth herein.

Examples 1-5 and 7-9 demonstrate active agent delivery systems containing a hydrophobic active agent having a relatively low (i.e., no greater than about 1200 g/mol) molecular weight.

Example 6 demonstrates an active agent delivery system containing a hydrophilic active agent having a relatively high (i.e., greater than about 1200 g/mol) molecular weight.

Example 10 demonstrates an active agent delivery system containing a hydrophilic active agent having a relatively low (i.e., no greater than about 1200 g/mol) molecular weight.

Example 1

Poly(carbonate urethane)/Poly(bis-phenol A carbonate) Blends with Dexamethasone (Hydrophobic Active Agent)

Blend Preparation and Miscibility Testing

Poly(carbonate urethane) 75D (PCU 75D) was purchased from Polymer Technology Group, Inc., Berkeley, CA. It is a copolymer of hydroxyl terminated polycarbonate, aromatic diisocyanate, and low molecular weight glycol. Poly(bis-phenol A carbonate) (PC), having a melt index (300°C/1.2 kg, ASTM D 1238) of 7 grams/10 minutes, was purchased from Sigma-Aldrich Co., Milwaukee, WI. Prior to blending, the two polymers were dried at 60°C to 70°C at reduced pressure overnight. The two dried polymers were dry-mixed at various ratios, followed by melt blending at about 200-225°C with a batch mixer (ThermoHaake, Karlsruhe, BW, Germany) equipped with two roller blades. The blending was conducted at 50 revolutions per minute (rpm). When the torque leveled off (within 2 to 3 minutes), the rpm was increased to 100. After the torque leveled off again (within 2 to 3 minutes), the rpm was set back to 50 rpm. Blending was continued for 1 more minute. After mixing was complete, the samples were collected and cooled to room temperature in air. In order to prevent oxidation during blending, 0.1-0.2 wt-% of IRGANOX 1010 antioxidant (Ciba Specialties Chemical Co., Terrytown, NY) was added into the blends before melt mixing.

The miscibility between PCU 75D and PC was tested by measuring the thermal transition temperatures of the blends from their mechanical properties. Film samples were prepared by pressing the blend samples between two hot plates at about 230°C for about 5 minutes. Typically, the films were about 0.1 millimeter (mm) to 0.5 mm thick, 5 mm to 7 mm wide, and 2 centimeters (cm) to 3 cm long. These films were mounted in a film/fiber fixture of a Rheometric Solids Analyzer III (RSAIII) (Rheometric Scientific, Inc., Piscataway, NJ). The initial gap was set to about 5 mm. Tests were done in dynamic mode at a

frequency of 1 Hz. The mechanical properties were recorded during heating the sample at a rate of 5°C/minute from -80°C to 200°C. The commanded strain was set to 0.1% from -80°C to 0°C, 0.5% from 0°C to 150°C, and 1% from 150°C to 200°C.

Figure 2 shows the storage modulus versus temperature. The modulus of pure PC started to drop at about 140°C. Therefore, the Tg of PC was about 140°C. Pure PCU had a similar transition that started at about 10°C until about 80°C. For the blends containing both PCU and PC, there were two glass transitions. As the content of PC increased, both of the Tg's increased and became closer together. This suggested that the PCU and PC were miscible.

Sample Preparation with Dexamethasone

Dissolution samples were prepared by solvent blending. Before dissolving PCU 75D poly(carbonate urethane) in THF, it was dried overnight at 70°C under reduced pressure, then melted and pressed between two hot plates at 230°C for 5-10 minutes. Then the films were cooled and placed in anhydrous tetrahydrofuran (THF) at about 60°C. The mixture was stirred with a magnetic bar until the polymer was dissolved. A small amount of gel was occasionally detected in solution, which was removed by filtering the solution with a 0.45-micron (μm) filter. The concentration of PCU was 1.16 wt-%. The PC was first dissolved in chloroform at room temperature to make a 5 wt-% solution. Then the solution was diluted with anhydrous THF to 1 wt-%. A 1 wt-% solution of dexamethasone (Sigma-Aldrich) in anhydrous THF was also made at room temperature. Then the three solutions were mixed at varying ratios to make different samples with the compositions shown in Table 2.

Table 2

PCU/PC (weight ratio)	100/0	90/10	80/20	70/30	50/50	30/70	0/100
Dexamethasone (wt-%) based on total solids	9.7	8.3	9.7	1.0	8.9	9.2	12.0

Dissolution samples were prepared with stainless steel (316L) shims that were cleaned by rinsing with THF. The cleaned shims were coated with a solution of 1 wt-% poly(ether urethane) (PELLETHANE 75D, Dow Chemical Co., Midland, MI) dissolved in THF. Before dissolving PELLETHANE 75D poly(ether urethane) in THF, it was dried overnight at 70°C under reduced pressure, then melted and pressed between two hot plates at 230°C for 5-10 minutes. Then the films were cooled and dissolved in anhydrous tetrahydrofuran (THF) at about 25°C by stirring with a magnetic bar overnight.

The coated shims were allowed to dry overnight under nitrogen. Subsequently, they were thermally treated at 215-220°C for 5-10 minutes. This pre-treatment led to formation of a primer on the surface of the shims that promoted their adhesion with polymer/active agent layers. The primer-treated shims were coated with the solutions listed above and dried overnight under nitrogen. The shims were weighed after each step. Based on the weight difference, the total amount of polymer/active agent coating was determined as was the thickness of the coating. A typical coating thickness was about 10 microns.

Dissolution of Dexamethasone

Dissolution of dexamethasone from PCU 75D/PC polymer matrix was conducted by placing the coated shims in glass vials that contained phosphate buffered saline solution (PBS, potassium phosphate monobasic (NF tested), 0.144 grams per liter (g/L), sodium chloride (USP tested), 9 g/L, and sodium phosphate dibasic (USP tested) 0.795 g/L, pH = 7.0 to 7.2 at 37°C, purchased from HyClone, Logan, UT).

Each shim had about 2 milligrams (mg) of coating (about 0.2 mg of dexamethasone) and each vial contained 3 milliliters (mL) of PBS. The vials were stored in an incubator-shaker at 37°C and agitated at about 50 revolutions per minute (rpm). The PBS was collected from the vials and replaced with fresh PBS. The concentration of dexamethasone was measured with a UV-Vis spectrophotometer (HP 4152A) that was calibrated with a series of dexamethasone solutions with known concentrations.

Dissolution Data Analysis

Figure 3 shows the cumulative release of dexamethasone increased with an increasing amount of PCU in the blend. These release curves clearly show that the release rate of dexamethasone could be adjusted by varying the content of PCU in the blends. Based on the curves, the diffusion coefficients of dexamethasone from these blends were calculated using the following equation and plotted as a function of blend composition in Figure 4.

$$D = \left(\frac{M_t}{4M_\infty}\right)^2 \cdot \frac{\pi x^2}{t}$$

wherein D = diffusion coefficient; M_t = cumulative release; M_∞ = total loading of active agent; x = the critical dimension (e.g., thickness of the film); and t = the dissolution time.

Figure 4 shows the log of the diffusion coefficient was almost a linear function of the blend composition, which demonstrated that the active agent release rate can be tuned by using miscible polymer blends. Additionally, the data presented in Figure 3 shows no burst, which indicates that the release of the active agent was predominantly under permeation control.

Example 2

Poly(ether urethane)/Phenoxy Blends with Dexamethasone (Hydrophobic Active Agent)

Poly (ether urethane) (PELLETHANE 75D) and dexamethasone were the same as that used in Example 1. Phenoxy resin (PX), a linear poly(bis-phenol A epoxide), was obtained from the Phenoxy Specialties Corp., Rockhill, CA). The grade used in the present example was PKHJ with a number average molecular weight of about 10-16 kilograms per mole (Kg/mol) and a Tg of 95°C. This material was expected to slow down the release rate of dexamethasone as the PC did in Example 1.

PELLETHANE 75D and dexamethasone were dissolved in THF as described in Example 1 (all the following procedures were the same as those used in Example 1 if not specified). PX was dissolved in anhydrous THF at room temperature with 1 wt-% of polymer in the solution. These three solutions were mixed at various ratios and coated onto stainless steel shims that were primer-treated in the same procedure as described in Example 1. After the coating dried, dissolution and UV-Vis analysis were conducted.

Cumulative release of dexamethasone from the PELLETHANE 75D/PX blend matrix was plotted in Figure 5. The release rate of dexamethasone increased with an increasing amount of PELLETHANE 75D in the blend. These release curves clearly show that by varying the contents of PELLETHANE 75D and PX, the release rate of dexamethasone was tuned. Additionally, the data presented in Figure 5 shows no burst, which indicates that the release of the active agent was predominantly under permeation control.

Miscibility between PELLETHANE 75D and PX was tested by measuring the Tg transitions of the PELLETHANE 75D/PX blends with a PYRIS 1 differential scanning calorimeter (DSC), PerkinElmer Company, Wellesley, MA. Solutions of about 5 wt-% PELLETHANE 75D and PX in THF were made separately using the same procedure as described above. The blend samples, each about 10 mg, were loaded into the

DSC and were scanned from -100°C to 230°C at 40°C/minute. Each sample was scanned twice. The second scan had less noise and was used. PYRIS software version 5.0 was used to determine the onset of Tg transitions. As shown in Figure 6, the pure PELLETHANE 75D had a glass transition at about 22°C and a melt-like transition at about 173°C. This Tg was considered to be associated with the hard domain of the resin. The Tg of the soft domain of poly(ether urethane), if it can be detected, is usually below 0°C. The pure PX had a Tg transition at a higher temperature (77°C). When PELLETHANE 75D and PX were blended, there were two changes. First, the Tg transitions of the pure PELLETHANE 75D and PX could no longer be clearly identified from the blend samples. There was a broader Tg transition range with a higher onset temperature compared to the Tg of the pure PELLETHANE 75D. This suggests that PELLETHANE 75D and PX are at least partially miscible (as defined herein). Second, there was a new transition representative of a crystalline component immediately after the Tg transition in all three blends. This suggests that PX caused a faster crystallization transition in PELLETHANE 75D, indicating the presence of interactions between PX and PELLETHANE 75D hard domains. This further supports the miscibility between the two materials.

Example 3

Poly(carbonate urethane) 75D/ Poly(carbonate urethane) 55D Blends with Dexamethasone (Hydrophobic Active Agent)

Poly(carbonate urethane) 75D (PCU 75D) and dexamethasone solutions were the same as that used in Example 1. PCU 55D is the trade designation for another member of the poly(carbonate urethane) family made by the Polymer Technology Group but softer than the PCU 75D polymer. It was dissolved in anhydrous THF in a similar procedure as that described in Example 1 for PCU 75D except the dissolution occurred at room temperature rather at 60°C. These three solutions were mixed at various ratios, coated onto stainless steel shims, and

dried using the same procedures described in Example 1. Dissolution tests were conducted as described in Example 1.

Cumulative release of dexamethasone from the PCU 75D/PCU 55D blends is shown in Figure 7. The release rate of dexamethasone increased with an increasing amount of PCU 55D in the blend. These release curves clearly show that by blending a softer (i.e., lower durometer) PCU into a harder one, the release rates of active agent could be increased.

It should be pointed out that the crossover between PCU 75D 100 with PCU 75D 70 was due to the thickness difference of the two. The release rates were determined by the initial linear region but not the later flat portions of the curves. Dexamethasone was released faster from PCU 75D 100 than from PCU 75D 70.

Example 4

Poly(ether urethane)/Phenoxy Resin with Rosiglitazone maleate (Hydrophobic Active Agent)

Rosiglitazone maleate, commercially available from Smithkline Beecham, United Kingdom, was released from PELLETHANE 75D/PX blends as described in Example 2. The blend compositions and all the sample preparation and test procedures were the same as those described in Example 2.

Cumulative release of this active agent was plotted in Figure 8. The release rate increased with an increasing amount of PELLETHANE 75D in the blend. These release curves clearly show that the release rate of rosiglitazone maleate was tuned by using miscible polymer blends.

Example 5

Polyvinyl Acetate (PVAC)/Cellulose Acetate Butyrate (CAB) With Dexamethasone

Thermal Stimulated Current (TSC) Test Method

Thermal stimulated current (TherMold Partners, L.P., Stamford, CT) was used to determine thermal transitions in PVAC/CAB blends. A piece of a film of about 1 centimeter (cm) by 1 cm was placed on the surface of a polytetrafluoroethylene (PTFE) film (about 50 microns thick). The two films were placed between the plate-pivot electrodes of the TSC. The testing chamber was purged by alternately turning on He gas (ultra high purity, Toll Gas and Welding Co., Plymouth, MN) and vacuum three times. The pressure of He was about 0.08 megapascal (MPa) to 0.12 MPa. After purging, the chamber was filled with He gas of the same pressure. The sample was heated to 200°C and a voltage of 200 Volts per millimeter (V/mm) was applied across the thickness of the sample and PTFE films. After 2 minutes, the sample was quenched to -50°C within about 10 minutes while the 200 V/mm of electric voltage was maintained. The electric field was then turned off and the sample heated at 2°C/minute to 200°C. Electric current across the films was recorded during this heating process. The recorded current-temperature curve was used to determine thermal transitions. As the PTFE film was used between the plate electrode and the sample film, one of its thermal transition peaks from 15-25°C appeared in the TSC curves of all the samples. In order to compare the thermal transition temperatures, the current was scaled such that the highest peak of each sample was reduced to 1. Therefore, the current values in the figures were in arbitrary units.

Sample Preparation with Dexamethasone

Polyvinyl acetate (PVAC, Mw (weight average molecular weight) = 167 to 500 killograms per mole (kg/mol)) and cellulose acetate butyrate (CAB, 29.5 wt-% acetyl and 17 wt-% butyryl, Mn (number

average molecular weight) = 65 kg/mol), both from Sigma-Aldrich Company, Milwaukee, WI, were dried in a vacuum oven and separately dissolved with anhydrous tetrahydrofuran (THF). The polymer concentration in both solutions was about 1 wt-%. A THF solution with 1 wt-% of dexamethasone (Sigma-Aldrich) was also made in a similar way. The three solutions were mixed in varying ratios to make 5 different samples with the compositions shown in Table 3.

Table 3

PVAC/CAB (weight ratio)	100/0	70/30	50/50	30/70	0/100
Dexamethasone (wt-%) based on total solids	10.8	10.6	10.1	10.4	9.7

Dissolution samples were prepared with stainless steel (316L) shims that were cleaned by rinsing with THF and dried. The cleaned shims were coated with a solution of 1 wt-% poly(ether urethane) (PELLETHANE 75D, Dow Chemical Co., Midland, MI) dissolved in THF. Before dissolving PELLETHANE 75D poly(ether urethane) in THF, it was dried overnight at 70°C under reduced pressure, then melted and pressed between two hot plates at 230°C for 5-10 minutes. Then the films were cooled and dissolved in anhydrous tetrahydrofuran (THF) at about 25°C by stirring with a magnetic bar overnight.

The coated shims were allowed to dry overnight under nitrogen then thermally treated at 215-220°C for 5-10 minutes. This pre-treatment formed a primer on the surface of the shim to promote adhesion with polymer/active agent layers. The primed shims were coated with the solutions listed above and dried overnight under nitrogen. The shims were weighed after each step. Based on the weight difference, the total amount of polymer/active agent coating was determined as was the thickness of the coating. Typical dissolution samples had 4-5 milligrams (mg) dried coating per shim that was about 10 microns thick.

Samples for miscibility tests were made in a similar way except that there was no primer coating. Typical sample thickness was about 100 microns and there was no active agent included therein.

Miscibility

Miscibility of PVAC and CAB was tested by measuring the thermal transition temperatures of various blends. Differential scanning calorimeter (DSC), dynamic mechanical analysis (DMA), and thermally stimulated current (TCS) were used to measure the glass transition temperature (Tg) and other transitions. TSC had the strongest signals. It provided consistent results as shown in Figures 9A-D. For the pure PVAC (Figure 9A), TSC showed two transition peaks, centered at 34°C and 62°C, respectively. Pure CAB (Figure 9A) had one peak centered at about 110°C in its TSC curve. When 30 wt-% of CAB was blended into PVAC, neither of the transition peaks of the PVAC was changed (Figure 9B). However, the glass transition of pure CAB disappeared, which suggests that this blend was miscible. When the amount of CAB was increased to 50 wt-%, the two transition peaks of PVAC shifted to higher temperature but no Tg peak for the pure CAB was observed (Figure 9C). This suggests that the PVAC and CAB were also miscible in 50/50 blend. In the blend containing 70 wt-% of CAB, the temperatures of the transition peaks were even higher, which once again suggests a miscible blend (Figure 9D). All of the films were clear and transparent, supporting our conclusion that these were miscible blends.

DSC analysis was conducted with PYRIS 1 DSC (PerkinElmer Company, Wellesley, MA). The scanning was programmed from -50°C to 220°C at 40°C/minutes. The sample size was about 10 milligrams (mg). As shown in Figure 10, the pure PVAC had a Tg transition at about 39°C and the pure CAB had a Tg at about 167°C. When PVAC and CAB were blended at a weight ratio of 70/30, the Tg corresponding to PVAC increased to 55°C. This suggested that the PVAC and CAB are partially miscible at this ratio. Adding more CAB, Tg corresponding to the PVAC further increased but at a slower rate. The Tg

corresponding to CAB decreased upon mixing with PVAC. All these results suggested that the PVAC and CAB are partially miscible over the entire range of mixing. This result was slightly different from that based on the TSC test described above. However, the conclusion using the miscibility definition of the present invention was the same, i.e., PVAC and CAB are miscible.

Dissolution of Dexamethasone

Dissolution of dexamethasone from PVAC/CAB polymer matrix was conducted with the polymer/active agent coated shims prepared as described above. The coated shims were cut into pieces, measured, and the areas were calculated for normalization. Each piece was immersed in a vial containing 3 millimeters (mL) of phosphate buffered saline solution (PBS, potassium phosphate monobasic (NF tested), 0.144 grams per liter (g/L), sodium chloride (USP tested), 9 g/L, and sodium phosphate dibasic (USP tested) 0.795 g/L, pH = 7.0 to 7.2 at 37°C, purchased from HyClone, Logan, UT). The amount of sample and PBS solution were chosen so that the concentration of active agent would be detectable by UV-Vis spectrophotometry, yet the concentration of active agent in the sample would not exceed 5% of the solubility of active agent in PBS (sink condition) during the experiment. Approximately 2 milligrams (mg) of coating, containing about 200 micrograms of active agent, and 3 milliliters (mL) of PBS that were preheated to 37°C were used. The dissolution test was run at 37°C and the samples were agitated on a shaker at about 10 cycles per minute. The PBS was removed from the sample vials and analyzed at various times to determine the concentration of active agent in each sample. The concentration of active agent in PBS was measured with UV-Vis spectroscopy (HP 4152A) at the wavelength of 243 nanometers (nm). The concentration of active agent in each sample was calculated by comparing to a standard curve created by a serial dilution method. The cuvette was carefully cleaned after each measurement to minimize accumulation of the hydrophobic active agent on the cuvette surface.

The cuvette was considered clean when the baseline was at least one order of magnitude lower than that of the measured active agent signal. The PBS was refreshed at each analysis time point.

Dissolution Data Analysis

Figure 11 shows the cumulative release of dexamethasone increased with an increasing amount of PVAC in the blend. These release curves clearly show that by blending PVAC and CAB, it was possible to vary the release rate by varying the relative amounts of two homopolymers. Based on the curves, the diffusion coefficients of dexamethasone from these blends were calculated using the following equation and plotted as a function of blend composition in Figure 12.

$$D = \left(\frac{M_t}{4M_\infty}\right)^2 \cdot \frac{\pi x^2}{t}$$

wherein D = diffusion coefficient; M_t = cumulative release; M_∞ = total loading of active agent; x = the critical dimension (e.g., thickness of the film); and t = the dissolution time.

The log of the diffusion coefficient was a linear function of the blend composition, demonstrating that the active agent release rate can be tuned by using miscible polymer blends. Additionally, the data presented in Figure 11 shows no burst, which indicates that the release of the active agent was predominantly under permeation control.

Example 6

Hydrophilic Polyurethane and a Poly(vinyl acetate-co-vinyl pyrrolidone) with Resten NG

TECOPHILIC HP-60D-60 polyurethane, Thermedics, Inc. Woburn, MA, and poly(vinyl acetate-co-vinyl pyrrolidone) (PVP-VA), Sigma-Aldrich Chemical Company, Milwaukee, WI, were the matrix

polymers used in this example. RESTEN NG, a 7000 molecular weight, water-soluble antisense oligonuctleotide, AVI Biopoharma, Corvallis, Oregon, was the active agent used in this example. The soft segment of TECOPHILIC polyurethane contains a mixture of poly(ethylene oxide) (PEO) and poly(tetramethylene oxide) (PTMO). The solubility parameter of this soft segment was estimated to be from 19 $J^{1/3}/cm^{3/2}$ (PTMO) to 23 $J^{1/3}/cm^{3/2}$ (PEO) based on Hoftyzer and van Kevelen's (H-vK) method (where the volumes of the chemicals were calculated based on Fedors' method) (Chapter 7, D.W.van Krevelen, Properties of Polymers, 3rd ed., Elsevier,1990, where Table 7.8 was for Hoftyzer and van Kevelen's method, Table 7.3 for Fedors' method). The solubility parameter of PVP-VA was estimated to be 23 $J^{1/3}/cm^{3/2}$ (molar average over PVP and VA monomers based on their mass ratio in polymer) based on the same method.

TECOPHILIC polyurethane was dissolved in anhydrous chloroform, Sigma-Aldrich Chemical Company, Milwaukee, WI, at a concentration of 1 wt-% polyurethane. The polyurethane and solvent were combined in a glass vial, which was sealed and shaken until the polyurethane was completely dissolved (by visual observation). Medtronic Model S-670 coronary stents (3.0 mm x 18 mm), which had previously been cleaned by ultrasonication in methanol and air dried, were spray coated with 50 to 100 micrograms of the polyurethane coating prepared above. A proprietary spray unit was used to coat the stents in this example, but any spray unit capable of applying a finely atomized mist of the polymer solution to the stent should be adequate. After spray coating with 50 to 100 micrograms of polyurethane solution, the stents were allowed to dry in lab ambient conditions, 25°C and 15% relative humidity (RH), for four hours. After the stents were dried they were placed in an oven at 220°C for 20 minutes to reflow the primer coating. After reflow the stents were removed from the oven and allowed to cool to room temperature.

TECOPHILIC polyurethane was dissolved in a solvent blend containing 80 wt-% anhydrous chloroform, Sigma-Aldrich Chemical

Company, Milwaukee, WI, and 20 wt-% anhydrous methanol, Sigma-Aldrich Chemical Company, Milwaukee, WI. The mixture was shaken until the polymer was completely dissolved (by visual observation). The concentration of TECOPHILIC in the solution was 1 wt-%. This solution is referred to as A.

RESTEN NG oligonuctleotide was dissolved in a solvent blend containing 80 wt-% anhydrous chloroform, Sigma-Aldrich Chemical Company, Milwaukee, WI, and 20 wt-% anhydrous methanol, Sigma-Aldrich Chemical Company, Milwaukee, WI. The mixture was shaken until the polymer was completely dissolved (by visual observation). The concentration of RESTEN NG in the solution was 1 wt-%. This solution is referred to as B.

PVP-VA was dissolved in a solvent blend containing 80 wt-% anhydrous chloroform, Sigma-Aldrich Chemical Company, Milwaukee, WI, and 20 wt-% anhydrous methanol, Sigma-Aldrich Chemical Company, Milwaukee, WI. The mixture was shaken until the polymer was completely dissolved (by visual observation). The concentration of PVP-VA in the solution was 1 wt-%. This solution is referred to as C.

The solutions A, B, and C were combined as shown in Table 4 below to make solutions with 1% overall "solids" concentration. The "solids" in each solution were comprised of 10 wt-% RESTEN NG and the remainder a blend of TECOPHILIC polyurethane and PVP-VA as denoted in Table 4.

Table 4

	Solution 1: 0% PVP-VA	Solution 2: 10% PVP-VA	Solution 3: 15% PVP-VA
A	2708 mg	2290 mg	2250 mg
B	315 mg	302 mg	302 mg
C	0	306 mg	461 mg

Solutions 1-3 were filtered with a 0.45-micron (microgram) filter and sprayed on the primed stents prepared above. The same

proprietary spray unit and process that was used to primed the stent was used to apply the top coat, although any spray unit capable of applying a finely atomized mist of the polymer and drug solution to the stent could have been used. The coated stents were dried at 45°C in a vacuum oven for 12 hours. Approximately 2000 micrograms (μg) of coating was applied to each stent, and the actual coating weight was used to calculate the theoretical amount of active agent on each stent based on the coating solution formulation.

Dissolution testing was conducted on the stents coated above. Each stent was placed in a vial with 3.0 milliliters (mL) of phosphate buffered saline solution (PBS, potassium phosphate monobasic (NF tested), 0.144 grams per liter (g/L), sodium chloride (USP tested), 9 g/L, and sodium phosphate dibasic (USP tested) 0.795 g/L, pH = 7.0 to 7.2 at 37°C, purchased from HyClone, Logan, UT) that was preheated to 37°C. The vials were stored in an incubator-shaker at 37°C and agitated at about 50 revolutions per minute. At designated times (1 minute, 1 hour, 3 hours, 1 day, 2 days, 3 days, and 4 days in this study) the entire volume of PBS was removed from the sample vial (the vial was quickly refilled with 3.0 mL of fresh PBS that was preheated to 37°C) and analyzed by UV-VIS Spectrophotometry (HP 4152A) at 260 nanometers (nm). The concentration of RESTEN NG in each sample was determined by comparision to a standard curve. The cumulative amount of RESTEN NG released was divided by the theoretical RESTEN NG load for each stent and plotted against square root time. The results are presented in Figure 13.

Although there was an initial burst of RESTEN NG released over the first hour, the remainder of the release curve was proportional to square root time indicating the RESTEN NG was released under permeation control. The rate of delivery correlated with the ratio of TECOPHILIC to PVP-VA in the matrix polymer blend. Coatings with more PVP-VA delivered RESTEN NG more quickly.

Miscibility between TECOPHILIC polyurethane and PVP-VA was tested with a PYRIS 1 differential scanning calorimeter (DSC),

PerkinElmer Company, Wellesley, MA. TECOPHILIC polyurethane and PVP-VA were dissolved in the same solvent and in the same way to make about 5 wt-% solutions. The two solutions were mixed at various ratios to make samples with the weight percentages of PVP-VA ranging from 0 to 100%. The blend samples were dried under protection of nitrogen gas. Before doing the test, the samples were further dried under reduced pressure at room temperature. The DSC scans were programmed from -100°C to 230°C at 40°C/minute. The samples were scanned twice. The second scan that had less noise were used. The sample size was about 10 milligrams (mg). The same procedure was used for all the Tg determinations in this example.

As shown in Figure 14, the pure TECOPHILIC polyurethane had a glass transition at about -53°C (onset temperature determined with PYRIS version 5.0 software). This Tg was considered to be associated with the soft domain. The Tg of the hard domain was higher than room temperature because this resin was fairly rigid at room temperature (Durometer 41D). The pure PVP-VA had a Tg transition at a higher temperature (76°C). When TECOPHILIC polyurethane was mixed with 20 wt-% of PVP-VA, its DSC curve was essentially not changed; but the Tg of PVP-VA disappeared. When the two polymers were mixed at a ratio of 50/50 by weight, the Tg transition of TECOPHILIC polyurethane disappeared. There was a very weak transition at the temperature around the Tg of PVP-VA. The disappearance of Tg transitions indicated that the two polymers were at least partially miscible.

Swelling tests were conducted with the same samples as for the DSC tests. Fully dried samples (Weight 1 = 50 to 100 mg) were put in a glass vial containing 5 mL of phosphate buffered saline solution (PBS, potassium phosphate monobasic (NF tested), 0.144 g/L, sodium chloride (USP tested), 9 g/L, and sodium phosphate dibasic (USP tested) 0.795 g/L, pH = 7.0 to 7.2 at 37°C, purchased from HyClone, Logan, UT). The vials were stored in an incubator-shaker at 37°C and agitated at about 50 revolutions per minute for about one day. The samples were taken out of the PBS. A piece of tissue was used to soak the free PBS from

sample surfaces. The samples were again weighed (Weight 2). Then, the samples were dried under reduced pressure at room temperature overnight. The samples were weighed for a third time (Weight 3). The swelling percentage was calculated by subtracting Weight 3 from Weight 2 and dividing by Weight 3. Pure TECOPHILIC polyurethane was swollen by about 56%. Pure PVP-VA was completely dissolved in PBS. The swelling percentage was plotted as a function of PVP-VA content in Figure 15 for the samples containing up to 20-wt% of PVP-VA. This clearly shows that increasing the PVP-VA content from 0 to 20 wt-% increases the swelling ratio of the blends from 56 to 101 wt-%. The weight loss (Weight 1- Weight 3) due to the leaching of PVP-VA into PBS was less than 1 wt-% for the samples containing no more than 10-wt% of PVP-VA.

Example 7

Poly(ethylene-co-methyl acrylate) (PEcMA)/Poly(vinyl formal) (PVM) with Dexamethasone (DX)

PEcMA and PVM were used in this example to control the release of dexamethasone (DX). The glass transition temperature, solubility parameter, molecular weight, vendor information for each of the polymers are listed in Table 5.

Table 5: Tg and solubility parameters for polymers. All data are from the vendor except where indicated.

Polymers	Tg (°C)	Solubility parameter ($J^{1/2}/cm^{3/2}$)	Notes	Sources
Poly (ethylene-co-methyl acrylate) (PEcMA)	7 (DSC)	16.9 [a]	d = 0.948 g/mL MA, 27 wt-% Mn = 13 kg/mol, Mw = 72.5 kg/mol	Sigma-Aldrich Co., Milwaukee, WI. Product No. 432660
Poly (vinyl formal) (PVM)	108	20.4 [c]	d = 1.23 g/mL	Sigma-Aldrich Co., Milwaukee,

				WI. Product No. 182680
Poly (styrene) (PS)	95	18.2 [b]	d = 1.04 g/mL Mw = 350 kg/mol Mn=170 kg/mol	Sigma-Aldrich Co., Milwaukee, WI. Product No. 441147
Poly (methyl methacrylate) (PMMA)	122	19.0 [c] 22.4 [b]	d = 1.17 g/mL Mw = 350 kg/mol	Sigma-Aldrich Co., Milwaukee, WI. Product No. 445746

a. Average of polyethylene (PE) and poly (methyl acrylate) (PMA) weighted by their molar percentages. The solubility parameters of PE and PMA were from D.W.van Krevelen, Properties of Polymers, 3rd ed., Elsevier, 1990. Table 7.5. Data were the average if there were two values listed in the sources.

b. D.W.van Krevelen, Properties of Polymers, 3rd ed., Elsevier, 1990. Table 7.5. Data were the average if there were two values listed in the sources.

c. The average of the calculated values based on Hoftyzer and van Kevelen's (H-vK) method (where the volumes of the chemicals were calculated based on Fedors' method) and Hoy's method. See Chapter 7, D.W.van Krevelen, Properties of Polymers, 3rd ed., Elsevier,1990, for details of all the calculations, where Table 7.8 was for Hoftyzer and van Kevelen's method, Table 7.3 for Fedors' method, and Table 7.9 and 7.10 for Hoy's method.

d. The solubility parameter of the VBVAVAC was an average mased on the molar percentages of the VB, VA, and VAC.

As the difference in the solubility parameters of the two polymers was about 3.5 $J^{1/2}/cm^{3/2}$, these two polymers were considered as miscible polymers as defined herein. Dexamethasone was also purchased from Sigma-Aldrich Co., Milwaukee, WI. The two polymers were dried at room temperature under reduced pressure overnight, and then were individually dissolved with anhydrous tetrahydrofuran (THF) (Sigma-Aldrich) to make 4 wt-% to 5 wt-% solutions. DX was dissolved using the same THF to make a solution of about 0.141 wt-%. The three

solutions were mixed in different amounts to make three blend solutions that contained about 0 wt-%, 40 wt-%, and 100 wt-% PEcMA, based on the total weight of solids.

Each solution contained about 10 wt-% DX, based on the total weight of solids. The blend solutions were coated on the surfaces of stainless steel (316L) shims of about 1.27 cm by 3.81 cm, which had previously been rinsed with THF and dried. The coated shims were stored under nitrogen gas at room temperature overnight to remove the solvent. The shims were weighed after each step of the experiment. Based on the weight differences, the total amount of drug/polymer coating was determined for each shim as was the thickness of the coating. In this example, the typical weight of the dried coating was about 4 milligrams (mg) to 10 mg per shim and the thickness was about 10 micrometers (microns) to 20 microns.

Dissolution of drug from PEcMA/PVM polymer matrix was conducted with the polymer/drug coated shims prepared above. The coated shims were cut into pieces that contained about 2 mg of coating. Each piece was immersed in a vial containing 3 milliliters (mL) of phosphate buffered saline solution (PBS, potassium phosphate monobasic (NF tested), 0.144 g/L, sodium chloride (USP tested), 9 g/L, and sodium phosphate dibasic (USP tested), 0.795 g/L, pH = 7.0 to 7.2 at 37°C, purchased from HyClone, Logan UT) that was preheated to 37°C. The dissolution test was run at 37°C and the samples were agitated on a shaker at about 10 revolutions per minute (rpm). The samples were analyzed at various times to determine the concentration of drug in the sample by collecting the PBS. After each collection, the PBS was refreshed. The concentration of DX in PBS was measured with UV-Vis spectroscopy (HP 4152A) at the wavelength of 243 nm. The concentration of DX in each sample was calculated by comparing to a standard curve created with a series of solutions of known concentrations.

Dissolution Data Analysis

Cumulative release of dexamethasone from the PEcMA/PVM blend matrix was plotted in Figure 16. The release rate of dexamethasone from PEcMA was much faster than that from PVM. The release rate for the miscible polymer blend was between that of the unblended polymers. These release curves clearly show that the release rate can be tuned by using a miscible polymer blend and adjusting the ratio of polymers in the blend. The cumulate release from all three matrices was almost linear with the square root of time, which indicates that there was no burst and the delivery of DX was under permeation control.

Example 8

Poly(ethylene-co-methyl acrylate) (PEcMA)/Polystyrene (PS) with Dexamethasone (DX)

PEcMA and PS were used in this example to control the release of DX. The glass transition temperature, solubility parameter, molecular weight, vendor information for each of the polymers are listed in Table 5. As the difference in the solubility parameters of the two polymers was about 1.3 $J^{1/2}/cm^{3/2}$, these two polymers were considered to be miscible polymers as defined herein. Dexamethasone was the same as that used in Example 7. Sample preparation, dissolution, and data analysis were the same as in Example 7. The release curves are shown in Figure 17. The release rate of dexamethasone was slower from PVM than from PEcMA. The release rate of DX from the miscible blend of PS and PEcMA was in between the rates of the unblended polymers. These release curves clearly show that the release rate can be tuned using a miscible polymer blend. The cumulative release of DX was proportional to the square root of time (no burst was observed) suggesting the delivery of DX from PEcMA/PS blends was under permeation control.

Example 9

Poly(ethylene-co-methyl acrylate) (PEcMA)/Poly(methyl methacrylate) (PMMA) With Dexamethasone (DX)

PEcMA and PMMA were used in this example to control the release of DX. The glass transition temperature, solubility parameter, molecular weight, vendor information for each of the polymers are listed in Table 5. As the difference in the solubility parameters of the two polymers was about 2.1 $J^{1/2}/cm^{3/2}$, these two polymers were considered to be miscible polymers as defined herein. Dexamethasone was the same as that used in Example 7. Sample preparation, dissolution, and data analysis were the same as described in Example 7. As shown in Figure 18, the release rate of DX from PEcMA was much faster than from PMMA. The release rate of DX from the miscible blend of PMMA and PEcMA was in between the rates of the unblended polymers. These release curves clearly show that the release rate can be tuned using a miscible polymer blend. The cumulative release of DX is also proportional to the square root of time (no burst was observed) suggesting the delivery of DX from PEcMA/PMMA blends was under permeation control.

Example 10

Poly(ether urethane) Blends with Coumarin (Hydrophilic Active Agent)

PELLETHANE 75D (PL75D), a poly(ether urethane), was purchased from Dow Chemical Company, Midland, MI. TECOPLAST (TP) (TP-470) and TECOPHILIC (TL) 60D60, other two poly(ether urethane)s, were purchased from Thermedics, Inc., Woburn, MA. TP has a Shore Hardness of 82D. Coumarin was purchased from Sigma-Aldrich Co., Milwaukee, WI. Based on the Merck Index (13 edit., Merck & CO., INC., Whitehouse Station, NJ), one gram of coumarin dissolves in 400 mL of cold water. Anhydrous tetrahydrofuran (THF), anhydrous

methanol, and acetonitrile (HPLC) used in this example were also purchased from Sigma-Aldrich Co., Milwaukee, WI.

PL75D was dried at 70°C at reduced pressure overnight. The dried pellets were compressed between two plates that were pre-heated to 230°C and maintained for about 5 minutes. After the sample was cooled down to room temperature, it was placed in a vial filled with THF and stirred until dissolved (by visual observation). TP and TL were directly dissolved in THF by stirring the mixtures at room temperature. Coumarin was also dissolved in THF. The concentrations of all the solutions were about 1 wt-%. TL solution and coumarin solution were mixed at a weigh ratio of 1:1. This mixture is the base coating solution of a reservoir system. TP solution and PL75D solution were mixed at various weight ratios to make five different mixtures with the weight ratios of TP to PL75D being 100:0, 75:25, 50:50, 25:75, and 0:100. These solutions are referred to herein as cap coating solutions of the reservoir system.

Dissolution samples were prepared with stainless steel (316L) shims (12.1 X 38.1 mm^2) that were cleaned by rinsing with THF. The cleaned shims were coated with the PL75D/THF solution. The coated shims were allowed to dry overnight under nitrogen. Subsequently, they were thermally treated at 215-220°C for 5-10 minutes. This thermal treatment led to formation of a primer on the surface of the shims that promoted their adhesion with polymer/active agent layers. The thickness of the primer coating was about 1 micrometer (micron). Five primer-treated shims were then coated with the base coating solution and dried overnight. Then, these shims were dip-coated with different cap coating solutions in the following way: the shim was dipped into one of the cap coating solutions for 2 to 3 seconds then was dried in nitrogen gas (for about 1 minute). Such dipping and drying processes were repeated for 8 times for each shim. The whole processes were completed in a nitrogen filled glove box. After completion of the coating, all five shims with different cap coating solutions were further dried in the

glove box overnight. The thickness of the cap coating in each shim was about 1.7 to 3.4 microns. All the coatings were clear and transparent.

Dissolution of Coumarin

Dissolution of coumarin from the cap-coated shims was conducted by placing the coated shims in glass vials that contained phosphate buffered saline solution (PBS, potassium phosphate monobasic (NF tested), 0.144 grams per liter (g/L), sodium chloride (USP tested), 9 g/L, and sodium phosphate dibasic (USP tested) 0.795 g/L, pH = 7.0 to 7.2 at 37°C, purchased from HyClone, Logan, UT). Each vial contained 4 milliliters (mL) of PBS. The vials were stored in an incubator-shaker at 37°C and agitated at about 50 rpm. The PBS was collected from the vials and replaced with fresh PBS at predetermined times. After one week, the dissolution tests were stopped and the remaining coating were dissolved in 4 mL of acetonitrile. The concentration of coumarin in all these solutions was measured with a liquid chromatography (HP 1090) that was equipped with a UV detector. Mobile phase was a mixture of 50 wt-% of sodium acetate water solution (pH=4) with 50 wt-% of acetonitrile (HPLC). The flow rate was 1.0 mL/minute. A Zorbax Eclipse (5 micron) column was used. The UV detection was conducted at a wavelength of 277 nm. The standard curve was obtained with a series of coumarin solutions with known concentrations. These standard coumain solutions were made by dissolving coumarin in methanol to make a concentrated solution (about 1 wt-%) and diluting this concentrated solution with PBS.

Dissolution Data Analysis

Cumulative percentage release of coumarin versus the PL75D content in the cap-coated shims was plotted in Figure 19. The total amounts of coumarin in the shims were determined by adding together all the coumarin in dissoluted solutions and that left in the remaining coatings. As was shown in the plot, coumarin was release much faster from a 100% PL75D coated shim than that from 100% TP coated shim.

The release rates from the PL75D/TP blends were between that from the two pure polymers. More interestingly, the rate was parallel to the PL75D content in the blends. These results clearly show that the release rate of coumarin could be adjusted by varying the composition of the blends.

Because the PL75D/TP blends were coated as a cap coating on the top of the TL/coumarin layer, we expected there would be time lag in the release curves. However, the result in Figure 19 did not show this. We speculate that this was because the TL/coumarin was re-dissolved during the dip coating process.

Miscibility Tests

The samples for miscibility tests were made to contain the same TP/ PL75D ratios as the dissolution samples had. There was no coumarin in these samples. The samples were scanned with a PYRIS 1 differential scanning calorimeter (DSC) (PerkinElmer Company, Wellesley, MA). The scanning was programmed from -100°C to 220°C at 40°C/min. The sample size was about 10 milligrams (mg) to 16 mg. As shown in Figure 20, the pure PL75D had a Tg transition at about 22°C and a melt-like transition at about 173°C. This Tg was considered to be associated with the hard domain of the resin. The pure TP had a glass transition at about 72°C. When PL75D and TP were blended at a weight ratio of 50/50, there was only one Tg transition that was at about 50°C. This suggested that the PL75D and TP are miscible at this ratio.

The complete disclosures of all patents, patent applications including provisional patent applications, and publications, and electronically available material cited herein are incorporated by reference. The foregoing detailed description and examples have been provided for clarity of understanding only. No unnecessary limitations are to be understood therefrom. The invention is not limited to the exact details shown and described; many variations will be apparent to one skilled in the art and are intended to be included within the invention defined by the claims.